GENDER AND THE GENOME
Volume 1, Number 4, 2017
Foundation for Gender-Specific Medicine
DOI: 10.1089/gg.2017.0016

COMMENTARY

Mitochondrial Replacement Techniques: Genetic Relatedness, Gender Implications, and Justice

Tetsuya Ishii, PhD[1] and César Palacios-González, PhD[2]

Abstract

In 2015 the United Kingdom (UK) became the first nation to legalize egg and zygotic nuclear transfer procedures using mitochondrial replacement techniques (MRTs) to prevent the maternal transmission of serious mitochondrial DNA diseases to offspring. These techniques are a form of human germline genetic modification and can happen intentionally if female embryos are selected during the MRT clinical process, either through sperm selection or preimplantation genetic diagnosis (PGD). In the same year, an MRT was performed by a United States (U.S.)-based physician team. This experiment involved a cross-border effort: the MRT procedure *per se* was carried out in the US, and the embryo transfer in Mexico. The authors examine the ethics of MRTs from the standpoint of genetic relatedness and gender implications, in places that lack adequate laws and regulation regarding assisted reproduction. Then, we briefly examine whether MRTs can be justified as a reproductive option in the US and Mexico, after reassessing their legalization in the UK. We contend that morally inadequate and ineffective regulations regarding egg donation, PGD, and germline genetic modifications jeopardize the ethical acceptability of the implementation of MRTs, suggesting that MRTs are currently difficult to justify in the US and Mexico. In addition to relevant regulation, the initiation and appropriate use of MRTs in a country require a child-centered follow-up policy and more evidence for its safety.

Keywords: mitochondrial replacement, gender, genetic relatedness, ethics

Introduction

Human cells harbor two different types of genomes. Inside the cells, more than 99.9% of DNA is localized in the nucleus, whereas the remaining 0.1% of DNA exists in mitochondria (termed nDNA and mtDNA, respectively). Mitochondrial functions are exerted through the coordinate expression of genes in the dual genomes of nDNA and mtDNA.[1] The most important function of the mitochondrion is probably the respiratory chain, by which cellular energy, adenosine triphosphate (ATP), is produced while precisely regulating the leakage of deleterious free radicals. To date, 13 mtDNA-encoded and 228 nDNA-encoded genes have been linked with the onset of mitochondrial DNA diseases (mtDNA diseases) in humans when mutated.[2] A human egg (oocyte) has as many as 200,000–300,000 copies of mtDNA per cell.[1] Because paternal mitochondria are digested after fertilization, wild-type or mutated mtDNA is maternally inherited to offspring, with at least 30 different mtDNA haplotypes.[3]

At present, mitochondrial replacement techniques (MRTs) are experimental nuclear transfer procedures where donor oocytes are used to reconstitute oocytes or zygotes with a reduced mtDNA mutation load. Briefly, the nuclear transfer is carried out between the affected intended mother's oocyte and an unaffected donor's oocyte (maternal spindle transfer; MST)[4–6] or between the intended parents' derived zygote and a donor zygote or a zygote created fertilizing a donor oocyte with a spermatozoon from the intended father (pronuclear transfer; PNT).[7,8] In October 2015, the United Kingdom (UK) became the first country to legalize MRTs to prevent the maternal transmission of serious mtDNA diseases to offspring, in instances where alternatives such as preimplantation genetic diagnosis (PGD) are clinically inapplicable.[9]

Around the same time as the legalization of MRTs took place in the UK, a group led by Dr. John Zhang, a fertility expert, performed MST for preventing a mitochondrial disease at their clinic in New York, and then shipped the only euploid embryo (of five created) to their affiliated clinic in

[1]Office of Health and Safety, Hokkaido University, Sapporo, Japan.
[2]Centre of Medical Law and Ethics, The Dickson Poon School of Law, King's College London, London, United Kingdom.

Guadalajara, Mexico.[6] This experiment resulted in the birth of a, so far, healthy boy. The parents, who seemed to have been insufficiently informed of potential risks of MST, decided to heavily limit follow-up examination of their child.[10] The cross-border nature of this experiment suggests the likelihood that scientists might try to break down the MRT procedure in such a way that it does not violate any local laws or regulations, even when the procedure as a whole might be banned in such places.[11,12]

MRTs raise a number of important ethical issues. First, although MRTs may offer a new reproductive opportunity for some women to have genetically related and unaffected children, the resultant children have mtDNA derived from an egg donor in addition to nDNA from parents, prompting the possibility of such children having three genetic parents. However, at this point in time it is uncertain how society will perceive this third genetic contributor. Second, MRTs have unique gender implications for the resultant children and oocyte donors. As MRTs remain experimental and subject to human technical dexterity,[4,5,7,8] their clinical use might fail to prevent the maternal transmission of an mtDNA disease. Third, MRTs can result in a form of human germline genetic modification that has been viewed as taboo in many countries.[13,14] Notably, a report by the US National Academies of Sciences (NAS) proposed a policy of transferring only male embryos in initial MRTs to prevent the occurrence of transgenerational risks.[15] Can such an embryo transfer policy truly justify the clinical use of MRTs? Finally, the implementation of MRTs requires oocyte donation, with its accompanying socioethical implications, as well as physical burdens and *possibly* health risks to egg donors.[13] The present article interrogates the ethics of MRT primarily from the standpoint of genetic relatedness and gender implications. Then, it analyzes whether MRTs can be justified in the US and Mexico, after reexamining the legalization in the UK after reexamining the legalization in the UK.

Genetic Relatedness

Women who have a pathogenic mtDNA mutation in their oocytes and who want to have genetically related children undergo a dire fate that deserves our sympathy. Sharon Bernardi is a living witness: She lost all seven of her children due to mitochondrial disease.[16] In the UK, MRTs legally offer a new reproductive opportunity for such women to have unaffected children who are genetically related to them, if there are no effective clinical alternatives. This effectively means that the reproductive freedom of such women is expanded. This *benefit to intended mothers* should not be confused with the supposed therapeutic benefit for living mitochondrial disease sufferers, which has been shown to be nonexistent.[17,18]

In addition to expanding the reproductive freedom of women wanting genetically related and healthy children, the genetic relatedness formed through MRTs must be also interrogated from the child's standpoint. MRTs introduce a new twist to the traditional academic debate regarding third party reproduction (i.e., using egg or sperm donors). In this study not only the assistance of a donor oocyte is essential but also it opens the important question of *how many* parents have children produced by MRTs. Consider, for example, how Alana Saarinen, 1 of 17 children born after donor ooplasmic transfer in the US, self-reports how she regards the person who provided the cytoplasm with which her mother's egg was ''augmented.'' Let us remember that in oocyte-cytoplasmic transfer cytoplasm from a donated oocyte is ferried into the intending mother's egg to make up for a presumptive ''ooplasmic deficiency.''[19] Alana said: ''I also have DNA from a third lady. But I wouldn't consider her a third parent.''[20] Her perception could be based on the fact that mtDNA accounts for only 0.1% of DNA in human cells and that mtDNA encodes only 13 respiratory chain proteins.[21]

It is possible that parents of children born from MRTs might consider that the ''genetic integrity'' of their children is equivalent to that of ''normally produced ones'' and, thus, that they only have two genetic parents. However, this would be a mistake since children who are a product of MRTs do have three genetic parents, contrary to what the Nuffield Council on Bioethics, the UK's Department of Health, and the UK's Human Fertilisation and Embryology Authority have asserted. We can defend the claim that such children have three genetic parents in the following way. The *amount* of mtDNA cannot be used as an argument against egg donors being genetic parents. To understand this, consider the following thought experiment: a scientist takes 1% of nDNA from 100 people and fuses it together, creating a healthy child. In this study we would say that such a child has 100 genetic parents. If this is true then we could further imagine the same scenario, but where the percentage of taken nDNA is 0.1% (the same percentage as that of mtDNA) from 1000 people. If it is true that this child has 1000 genetic parents, no matter how wild this sounds, then we have to accept that the egg donor in MRT scenarios is a genetic parent too.[22] One might rebut that mtDNA, which contributes to only 0.1% in human genome, as such, does not play a significant role in genetic parenthood. However, if we think that only the transfer of genetic material that confers ''personal characteristics'' establishes genetic parenthood then we have to accept that egg donors in MRT cases are genetic parents. They are so because the mitochondria, contained in the donated enucleated eggs, are a fundamental piece in ''conferring'' health, which is a personal characteristic.

Children born from MRTs are different from children born following infertility treatment using donor gametes in terms of the genetic parenthood uniquely formed by the MRT. Unlike Alana, some children born from MRTs might acknowledge egg donors as genetic parents, demanding from them what is legally and morally required from egg and sperm donors. Furthermore, this novel genetic composition opens the question of whether or not clinics should offer counseling services to such children as part of the follow-up treatment.

Gender Implications

MRTs have other specific gender implications for the resultant children and oocyte donors. Let us begin with the gender implications of MRTs, as the Genetic Relatedness section calls for great insight from the standpoint of the resultant children. It is a truism that there is no medicine without risks, and MRTs are not the exception. MRTs might fail to prevent the maternal transmission of a pathogenic mtDNA mutation to the resultant offspring.[4,5,7,8] Furthermore, even if children born after MRTs do not develop life-threatening disease, some females might undergo the same

fate as their mothers: they could be at risk of transmitting a mtDNA disease to their future children (just as women who are not affected by a mtDNA disease but who have a pathogenic mtDNA mutation in their oocytes). For this, and to avoid ''crossing the germline,'' a report by the US NAS proposed a policy of transferring only male embryos in initial MRTs.[15] This, according to them, would avoid imposing harms to subsequent generations. Seemingly, this policy could be compared with the use of PGD to avoid sex-linked diseases by selecting embryos of a particular chromosomal sex.[23] In PGD a cell from a cleaving embryo, or blastocyst, is harvested to perform a genetic analysis. However, the selection of male embryos through PGD after an MRT, when this was not done through sperm sorting, requires an additional invasive procedure[24] (in addition to the nuclear transfer) which reduces the overall number of potential embryos for transfer (i.e., female embryos are selected against), and which could lead to implantation loss.[25] Moreover, it is unknown if the combined use of MRT and PGD might increase the risk that offspring are born with an impairment, which would clearly go against the intended mother's, or couple's, goal of having a healthy genetically related child.[26,27]

Finally, the policy of only male embryo transfer could send a problematic message to society: Those male children, as the first generation following an MRT, should take the entire risk of this experimental procedure. Consider another policy of only female embryo transfer: Such female children should take an even greater risk, because mtDNA is maternally inherited by future offspring. Such gender-biased uses of MRTs would be problematic. The clinical use of MRTs should be considered after the potential risks were sufficiently minimized through preclinical research, regardless of the future child's gender.

The aforementioned argument primarily focused on prospective parents and children who benefit from MRTs. Next, we consider gender issues relevant to the egg donors, both for MRT research and clinical practice.[28] Because research and the clinical practice of MRTs require oocytes donated by healthy third-party women, it is crucial to properly consider the possible health risks to such donors. As oocyte retrieval is practiced with the use of several medications, hormonal injection, and transvaginal aspiration, it has been argued that female donors may be financially compensated for such burden, distress, and potential health risks.[29] Importantly, egg donation could not only be motivated by mere financial or altruistic objectives, but also could be so by the aim of securing other goods, for example, having a niece, nephew, or grandchild (as suggested by father-to-son sperm donation[30]).

The *short-term* health risks of egg extraction are not so high if well practiced. For example, the occurrence of severe ovarian hyperstimulation syndrome is 0.2–1%.[31] Nevertheless, there are no quality *long-term* studies about the health risks that egg donation might impose on young egg donors. Recently, Schneider *et al.* have raised the question of whether breast cancer risk follows oocyte retrieval.[32] Their question stems from four clinical cases where young women donated eggs and then, after some years, developed breast cancer. If MRTs are to move forward in an ethical way then the appropriate measures should be in place for making it clear in the egg donation consent forms, regardless of jurisdiction, that there are no known data about the long-term health risks of egg donation for young donors. This is of paramount importance since otherwise the egg donor's informed consent would be defective (i.e., it wouldn't be really autonomous). If egg donation does take place then the egg donors should have the option of close follow-up. Establishing local or national (voluntarily) registries of egg donors would facilitate such long-term observation.

In its current practice worldwide, oocyte donation has also raised important ethical question with regard to exploitation and the commodification of eggs.[13,33] Unlike sperm produced in men, oocytes are no longer regenerated in women after birth, thus decreasing the number of oocytes with every ovulation until menopause. Moreover, financial compensation may be arranged for egg donors, because oocyte retrieval involves potential health risks, medical costs, loss of time or wage, as addressed above. However, the transaction of such precious reproductive cells at higher prices has prompted profound concern in some countries. This worry has been exacerbated when people from affluent countries travel to developing areas to acquire oocytes for reproductive purposes.

A policy of morally acceptable compensation for a limited number of oocyte donations per one individual would help prevent the exploitation of women. A donor registry would further protect them by ensuring the possibility of long-term follow-up. Concerns over oocyte donation required *for MRT* would not become a substantive public health issue if MRTs were authorized at least initially only for rare and serious cases, although such restriction would require additional argument in its favor.[34] But even if this were the case our recommendations regarding egg donation would still stand given the amount of women that donate their eggs for third party reproduction. The total amount of risk to living donors could also be diminished or eradicated if practitioners relied on other egg sources, such as those from cadaveric donation.

Finally, several research articles published after the legalization in the UK highlighted the *possibility* that MST and PNT may fail to prevent mitochondrial disease in offspring, especially if matching patient's nDNA and donor's mtDNA haplotype is not meticulously considered, although this is a heavily contested point.[4,5,7,8] Of note, the report on the first MST admitted that mtDNA haplotype of the oocyte donor (L2c) was different from that of the patient (I).[6] Matching patient's nDNA and donor's mtDNA make it difficult to find appropriate egg donors for MRT, but can potentially contribute to the prevention of mitonuclear mismatch.

Legitimacy in the UK, the US, and Mexico

The UK already has a policy on compensation for oocyte donors (up to £750 per donation cycle) and for an egg donor registry system. It also intends to secure contact information for children born from conception using donor gametes.[35] The regulation of PGD for preventing genetic diseases on a condition-by-condition basis has already been established in the country.[36] And, after nationwide discussions, the UK determined that only licensed clinics can provide MRTs as an option for range of limited cases, and they did not adopt

the policy of male-only embryo transfer.[37] Moreover, the country decided to require physicians to prepare a follow-up scheme for MRT conceived children, but allowed parents not to consent to the follow-up of their child.[38] Thus it is unlikely that any significant socioethical problems will arise regarding the use of MRTs in the UK, except with the status of the egg donor and the policy of voluntary follow-up of the resultant children.

In contrast, the cross-border case of an MST alerts us of the possibility of its widespread use in an imperfect way in the world because of different regulatory standards. In the US, the American Society for Reproductive Medicine (ASRM) issued guidelines on financial compensation of oocyte donors,[39] stating that ''Total payments to donors in excess of $5,000 require justification and sums above $10,000 are not appropriate.'' However, the ASRM guidelines are nonbinding policy by a professional society. Countrywide states' statutes on oocyte donation are either not enacted or vary from state to state, excluding some states such as Louisiana that prohibits the sale of human oocyte.[40] At federal level, oocyte donation is largely allowed. Therefore, the possibility of ''exploitation and commodification of eggs'' is more likely to occur in the US.[41] In addition, in the US there are no national regulations regarding the use of PGD, unlike the UK.[42]

Congress passed the Consolidated Appropriations Act 2016 Sec. 749 in the end of 2015 (still effective in Consolidated Appropriations Act 2017 Sec. 736), which prohibits the FDA from spending federal budget to *review applications* regarding clinical trials in which ''a human embryo is intentionally created or modified to include a heritable genetic modification.''[43] And more recently, the US-based physician, who performed the cross-border MST, established a company to offer MST to treat infertility, outside of the US, for women in their 40s.[44] At this point in time, clinically offering MST for treating infertility cannot be justified, because there is no clear evidence to suggest that mtDNA mutations due to old age are causative of infertility.[45] Finally, on August 4, 2017 the FDA sent Dr. Zhang a strong worded letter pointing out various regulation violations that Dr. Zhang's team incurred on when they carried out MST, and they also pointed out that Zhang's company ''Darwin Life'' kept on marketing MRTs within the US even when they have said that they would stop doing so.[46]

Mexico currently lacks national regulations pertaining to assisted reproduction. This means that there are no national regulations concerning oocyte donation or PGD.[12,47] In addition, although the legality of the first MST is controversial, Mexico has no explicit federal regulations concerning the regulation of human germline genetic modification or human genetic engineering.[11,12,48]

Again, consider the process of the first MST case led by Dr. Zhang. They performed MST at their clinic in the US and then shipped the euploid embryo to their affiliated clinic in Mexico, in which the embryo was transferred to a Jordanian woman. The FDA warned that if practitioners intend the marketing of MRT in the US then they need to obtain a valid biologics license (for embryos made through MST in this case) and provide supporting data that should be obtained after approved clinical research. However, the first MST case was considered to be research, not marketing of biologics. In addition, the Consolidated Appropriations Act 2016 does not prohibit private-funded research in which oocytes are reconstituted by MST and fertilized but not used for embryo transfer in the US. Meanwhile, Mexico has no explicit regulations relevant to the clinical use of such modified embryos. If the boy born through MST develops any health problems, the Jordanian parent can institute a civil action in a court in Mexico. However, the legal proceedings may go against the parents because the parents declined the follow-up examination of their boy.

The regulatory situations surrounding reproductive medicine in the US and Mexico suggest that we cannot make an overall national moral assessment of the clinical practice of MRTs, and thus, a case-by-case assessment of the morality of MRTs must be carried out. Advertisements on reproductive tourism websites already present four clinics (in Albania, Israel, Russia, and Spain) that offer ''nuclear transfer'' as an available treatment.[49] Such advertisements, as well as the cross-border use of MST, urge us to respond to the unregulated use of MRT in each country.

Conclusion

The initiation and appropriate use of MRT in a country should require the premise that oocyte donation is morally acceptable and appropriately regulated. The current state of MST and PNT underscores the need for further research, as well as long-term follow-up of such children, in addition to the urgent need of long-term studies regarding possible health risks to young egg donors. More preclinical research is required to improve the safety and efficacy of MRT. The UK adopted the policy of voluntary follow-up of children born from MRTs. However, the follow-up should be conducted in a child-centered manner, requiring the mandatory follow-up for at least several years or until they are legally competent to refuse it. It must be noted that troubles in the family structure, such as divorce and parental death, may make follow-up difficult. To respond to the likelihood of the widespread use of MRT in the world, the public, professionals, ethicists, and policy makers should consider the appropriateness and regulation of MRT.

Acknowledgments

This research was supported by JSPS KAKENHI Grant Number 26460586 (T.I.) and the Wellcome Trust through a Senior Investigator Award in Ethics and Society: The Donation and Transfer of Human Reproductive Materials, grant number: 097897/Z/11/Z (C.P.G).

Author Disclosure Statement

No competing financial interests exist.

References

1. Ishii T. Mitochondrial manipulation for infertility treatment and disease prevention. In: Schatten H, ed. Human reproduction: updates and new horizons. New Jersey: Wiley Blackwell; 2016. p. 205–230.
2. Koopman WJ, Willems PH. Smeitink JA. Monogenic mitochondrial disorders. N Engl J Med 2012;366:1132–1141.
3. van Oven M, Kayser M. Updated comprehensive phylogenetic tree of global human mitochondrial DNA variation. Hum Mutat 2009;30:E386–E394.

4. Yamada M, Emmanuele V, Sanchez-Quintero MJ, et al. Genetic drift can compromise mitochondrial replacement by nuclear transfer in human oocytes. Cell Stem Cell 2016; 18:749–754.
5. Kang E, Wu J, Gutierrez NM, et al. Mitochondrial replacement in human oocytes carrying pathogenic mitochondrial DNA mutations. Nature 2016;540:270–275.
6. Zhang J, Liu H, Luo S, et al. Live birth derived from oocyte spindle transfer to prevent mitochondrial disease. Reprod Biomed Online 2017;34:361–368.
7. Zhang J, Zhuang G, Zeng Y, et al. Pregnancy derived from human zygote pronuclear transfer in a patient who had arrested embryos after IVF. Reprod Biomed Online 2016; 33:529–533.
8. Hyslop LA, Blakeley P, Craven L, et al. Towards clinical application of pronuclear transfer to prevent mitochondrial DNA disease. Nature 2016;534:383–386.
9. UK_Department_of_Health. The Human Fertilisation and Embryology (Mitochondrial Donation) Regulations 2015 www.legislation.gov.uk/ukdsi/2015/9780111125816/contents (accessed March 30, 2017).
10. Alikani M, Fauser BCJ, García-Valesco JA, et al. First birth following spindle transfer for mitochondrial replacement therapy: hope and trepidation. Reprod Biomed Online 2017; 34:333–336.
11. Palacios-González C, de Jesús Medina-Arellano M. Mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case. J Law Biosci 2017;4:50–69.
12. Ishii T. Peer Commentary: mitochondrial replacement techniques and Mexico's rule of law: on the legality of the first maternal spindle transfer case. J Law Biosci 2017. DOI: 10.1093/jlb/lsx015.
13. Baylis F. The ethics of creating children with three genetic parents. Reprod Biomed Online 2013;26:531–534.
14. Ishii T. Potential impact of human mitochondrial replacement on global policy regarding germline gene modification. Reprod Biomed Online 2014;29:150–155.
15. US_NAS_Committe. In: Claiborne A, English R, Kahn J, eds. Mitochondrial replacement techniques: ethical, social, and policy considerations. (National Academies Press (US) Copyright 2016 by the National Academy of Sciences. All rights reserved, 2016).
16. BBC_News. The woman who lost all seven children. 2012. www.bbc.com/news/magazine-19648992 (accessed August 29, 2017).
17. Rulli T. What is the value of three-parent IVF? Hastings Cent Rep 2016;46:38–47.
18. Palacios-Gonzalez C. Are there moral differences between maternal spindle transfer and pronuclear transfer? Med Health Care Philos 2017;20:503–511.
19. Chen SH, Pascale C, Jackson M, et al. A limited survey-based uncontrolled follow-up study of children born after ooplasmic transplantation in a single centre. Reprod Biomed Online 2016;33:737–744.
20. BBC_News. The girl with three biological parents. 2016. www.bbc.com/news/magazine-28986843 (accessed August 29, 2017).
21. Anderson S, Bankier, AT, Barrell BG, et al. Sequence and organization of the human mitochondrial genome. Nature 1981;290:57–65.
22. Palacios-González C. Does egg donation for mitochondrial replacement techniques generate parental responsibilities? J Med Ethics 2017. DOI:10.1136/medethics-2017-104400.
23. SenGupta SB, Dhanjal S, Harper JC. Quality control standards in PGD and PGS. Reprod Biomed Online 2016;32: 263–270.
24. Bredenoord AL, Dondorp W, Pennings G, et al. Avoiding transgenerational risks of mitochondrial DNA disorders: a morally acceptable reason for sex selection? Hum Reprod 2010;25:1354–1360.
25. Stern H. Preimplantation genetic diagnosis: prenatal testing for embryos finally achieving its potential. J Clin Med 2014; 3:280.
26. Reinhardt K, Dowling DK, Morrow EH. Medicine. Mitochondrial replacement, evolution, and the clinic. Science 2013;341:1345–1346.
27. Sampino S, Zacchini F, Swiergiel AH, et al. Effects of blastomere biopsy on post-natal growth and behavior in mice. Hum Reprod (Oxford, England) 2014;29:1875–1883.
28. Haimes E, Taylor K. Rendered invisible? The absent presence of egg providers in U.K. debates on the acceptability of research and therapy for mitochondrial disease. Monash Bioeth Rev 2015;33:360–378.
29. Wilkinson S. Is the HFEA's policy on compensating egg donors and egg sharers defensible? Med Law Rev 2013;21: 173–212.
30. Bredenoord AL, Lock MT, Broekmans FJ. Ethics of intergenerational (father-to-son) sperm donation. Hum Reprod (Oxford, England) 2012;27:1286–1291.
31. Binder H, Dittrich R, Einhaus F, et al. Update on ovarian hyperstimulation syndrome: Part 1—incidence and pathogenesis. Int J Fertil Womens Med 2007;52:11–26.
32. Schneider J, Lahl J, Kramer, W. Long-term breast cancer risk following ovarian stimulation in young egg donors: a call for follow-up, research and informed consent. Reprod Biomed Online 2017;34:480–485.
33. Brandt R, Wilkinson S, Williams N. The donation and sale of human eggs and sperm. In: Zalta EN, ed. The Stanford Encyclopedia of Philosophy. https://plato.stanford.edu/entries/gametes-donation-sale/ (accessed December 13, 2017).
34. Palacios-Gonzalez C. Mitochondrial replacement techniques: egg donation, genealogy and eugenics. Monash Bioeth Rev 2016;34:37–51.
35. Human Fertilisation & Embryology Authority (HFEA). Donating your eggs. 2017. www.hfea.gov.uk/donation/donors/donating-your-eggs (accessed August 30, 2017).
36. Human Fertilisation & Embryology Authority (HFEA). PGD conditions. 2017. www.hfea.gov.uk/pgd-conditions (accessed August 30, 2017).
37. Human Fertilisation and Embryology Authority (HFEA). Mitochondrial Replacement Consultation: advice for Government. s.6.19. HFEA, London; 2013.
38. Human Fertilisation and Embryology Authority (HFEA). Mitochondrial donation treatment. 2017. www.hfea.gov.uk/treatments/embryo-testing-and-treatments-for-disease/mitochondrial-donation-treatment (accessed August 30, 2017).
39. Ethics Committee of the American Society for Reproductive Medicine (ASRM). Financial compensation of oocyte donors. Fertil Steril 2007;88:305–309.
40. RS 9:122: Uses of human embryo in vitro. Louisiana State Legislative Law 1986.
41. Kenney NJ, McGowan ML. Looking back: egg donors' retrospective evaluations of their motivations, expectations, and experiences during their first donation cycle. Fertil Steril 2010;93:455–466.

42. Bayefsky MJ. Comparative preimplantation genetic diagnosis policy in Europe and the USA and its implications for reproductive tourism. Reprod Biomed Soc Online 2017. DOI: 10.1016/j.rbms.2017.01.001.
43. Cohen IG, Adashi EY. SCIENCE AND REGULATION. The FDA is prohibited from going germline. Science 2016; 353:545–546.
44. Mullin E. The Fertility Doctor Trying to Commercialize Three-Parent Babies. MIT Technology Review. 2017. www.technologyreview.com/s/608033/the-fertility-doctor-trying-to-commercialize-three-parent-babies (accessed December 09, 2017).
45. Demain LA, Conway GS, Newman WG. Genetics of mitochondrial dysfunction and infertility. Clin Genet 2017;91: 199–207.
46. The_FDA. August 4, 2017-Letter to Darwin Life Inc. 2017. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ComplianceActivities/Enforcement/UntitledLetters/UCM570225.pdf? (accessed August 9, 2017).
47. International Federation of Fertility Societies. IFFS Surveillance 2016. Global Reprod Health 2016;1:1–143.
48. Palacios-González C, Medina-Arellano MDJ. Author's Response to Peer Commentaries: Mexico's rule of law and MRTs. J Law Biosci 2017:lsx031. DOI:10.1093/jlb/lsx031.
49. IVF_Clinics_Worldwide_website. Clinics offering ''nuclear transfer''. 2017. www.ivfclinicsworldwide.com/fertility-clinics/?clinic_country=&treatments_select=nuclearTransfer&title= (accessed August 29, 2017).

Address correspondence to
Tetsuya Ishii, PhD
Office of Health and Safety
Hokkaido University
Kita 8, Nishi 5, Kita-ku
Sapporo 060-0808
Japan

E-mail: tishii@general.hokudai.ac.jp

Received for publication September 11, 2017; received in revised form November 12, 2017; accepted November 21, 2017.